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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FREDERICK J. HAMBLE, ESQ.
712 KITCHAWAN ROAD
OSSINING, NY 10562

EXAMINER	
LI, RUIXIANG	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,694	BRINES ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14,16-21,31,32 and 43-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13, 14, 16-21, 31, 32, 43-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/28/2008 has been entered. Claims 13, 21, 43-47, 49 are amended. Claims 51-54 are added. Claims 13, 14, 16-21, 31, 32, 43-54 are pending and under consideration.

Withdrawn Objections and/or Rejections

The rejection of claims 13, 14, 16-21, 31, 32, and 43-50 under 35 U.S.C. 112, first paragraph for scope of enablement is withdrawn in view of amended claims.

The rejection to claims 13, 14, 16-20, 31, 32, 43-50 under 35 U.S.C. §112, second paragraph is withdrawn in view of Applicants' argument.

Claim Rejections under 35 USC § 112, 1st paragraph

(i). The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(ii). Claims 13, 14, 16-2, 31, 32, and 43-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using an EPO receptor and a βc receptor complex in screening assays to identify a compound that inhibits apoptosis in cardiomyocytes, does not reasonably provide enablement for a method of identifying a compound that exhibit a tissue protective activity, wherein the tissue protective activity inhibits damage/death of tissue or organ, or any types of cells other than cardiomyocytes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 13, 14, 16-20, 21, 31, 32, and 43-54 are drawn to a method for identifying a compound that modulates a tissue activity using an EPO receptor and a βc receptor complex. The specification states that the term "tissue protective activity" refers to "the effect of inhibiting or delaying damage or death of a cell, tissue, or organ. The tissue

activity can be against various conditions, disease, and cellular, organ, and/or tissue damage, for example, those described in section 5.5" (page 13). Thus, the claims are broad and encompass a method of identifying a compound that exhibits a broad range of tissue protective activities.

The instant disclosure merely discloses that the percent apoptosis for βc (-/-) cardiomyocyte cells where apoptosis was induced by incubating with staurosporine in the presence of EPO did not significantly differ from the percent apoptosis in wild type and βc (-/-) cardiomyocyte cells in the absence of EPO (Example 6.5). These results suggest that inhibition of apoptotic cell death induced by incubating with staurosporine is dependent on the presence of a βc receptor in cardiomyocyte cells. However, the specification does not provide sufficient guidance and/or working examples regarding on how to identify a compound that modulates a tissue protective activity other than inhibition of apoptosis in cardiomyocyte cells. The prior art teaches a functional role of βc in the EPO-dependent proliferation of Ba/F3 cells that express EPO-R (Jubinsky et al., Blood 90:1867-1873, 1997). However, there are no teachings on a method of identifying a compound that exhibit a tissue protective activity, wherein the tissue protective activity inhibits damage/death of tissue or organ.

It is unpredictable whether a compound identified based upon the instantly claimed screening method that exhibit a tissue protective activity, wherein the tissue protective activity inhibits damage/death of tissue or organ. Accordingly, it would take undue

experimentation for one skilled in the art to practice the claimed method commensurate in scope with these claims.

Claim Rejections Under 35 U. S. C. § 103 (a)

(i). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(ii). Claims 13, 14, 17, 19, 20, 48, 49, and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jubinsky et al. (Blood 90:1867-1873, 1997) in view of Mercury™ Pathway Profiling System User Manual (Clontech, March 2, 2001).

Jubinsky et al. teach a functional complex comprising EPO receptor (EPO-R) and a common β chain (βc) in murine Ba/F3 cells which were transfected with either murine EPO-R or EPO-R/βc. The Ba/F3 wild-type cells endogenously express IL-3Rα (and thus βc). Jubinsky et al. teach a functional role of βc in the EPO-dependent proliferation of Ba/F3 cells that express EPO-R (last paragraph of the article) and that both Ba/F3-EPO-R and Ba/F3-EPO-R+βc required EPO for survival and responded to EPO (see,

e.g., bottom of right column of page 1868; Fig. 1) and a functional role of βc in the EPO-dependent proliferation of Ba/F3 cells that express EPO-R. Jubinsky et al. teach a method for identifying the effect of antisense to βc, sense, and nonsense on EPO-dependent proliferation and β globin expression in Ba/F3 cells (page 1869; Fig. 2).

Jubinsky et al. fail to teach transfection of the cells with a nucleic acid comprising a nucleotide sequence that encodes a reporter gene operably lined to a regulatory element associated with a tissue protective cytokine receptor complex activity and detect the changes in the level of reporter gene expression as recited in step (a) and (b) of claim 13

Mercury™ Pathway Profiling System User Manual teaches reporter genes-- SEAP and luciferase, various vectors containing a promoter and a response element, including E2F, SRE controlling the transcription of the SEAP gene or luciferase gene (Table 1 and Fig. 2), and an assay of screening a compound for its effect based upon the reporter activity (Fig. 1).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Jubinsky et al. by inclusion of the reporter system described in the Mercury™ Pathway Profiling System User Manual with a reasonable expectation of success. One would have been motivated to do so because the reporter system described in the Mercury™ Pathway Profiling System User Manual

provides an ideal reporter for signal transduction and proliferation linked to activation of a membrane receptor (see, e.g., Fig. 1 and Fig. 2). It is noted that the compound that modulates the activity of the EPO-R/βc complex screened by the method taught by the cited art would necessarily have the properties cited in claims 51-54.

(iii). Claims 13, 16-18, 21, 43-48, and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jubinsky et al. (Blood 90:1867-1873, 1997) in view of Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000).

Jubinsky et al. teach a functional complex comprising EPO receptor (EPO-R) and a common β chain (βc) in murine Ba/F3 cells which were transfected with either murine EPO-R or EPO-R/βc. The Ba/F3 wild-type cells endogenously express IL-3Rα (and thus βc). Jubinsky et al. teach a functional role of βc in the EPO-dependent proliferation of Ba/F3 cells that express EPO-R (last paragraph of the article) and that both Ba/F3-EPO-R and Ba/F3-EPO-R+βc required EPO for survival and responded to EPO (see, e.g., bottom of right column of page 1868; Fig. 1) and a functional role of βc in the EPO-dependent proliferation of Ba/F3 cells that express EPO-R. Jubinsky et al. teach a method for identifying the effect of antisense to βc, sense, and nonsense on EPO-dependent proliferation and β globin expression in Ba/F3 cells (page 1869; Fig. 2).

Jubinsky et al. fail to teach (i). that the tissue protective cytokine receptor complex-expressing cell is a prokaryotic cell, a human cell, or a modified yeast cell, as recited in claims 16, 18, and 21; and (ii). that the test compound is a small molecule, a peptide, a member of library, an antibody, or a compound that binds the tissue protective cytokine receptor complex ligand, as recited in claims 43-47 and 50.

Trueheart et al. teach rapid, reliable and effective assays for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate the activity of a heterologous receptor (column 2, the 3rd paragraph and last paragraph; 2nd paragraph of column 13), including cytokine receptor (see, e.g., the 3rd paragraph of column 20). Trueheart teach that the cells used in the assay can be any type of cells, whether prokaryotic or eukaryotic, including yeast cells, mammalian cells, such as HeLa cell that is a human cell (column 2, 4th paragraph; column 15, last two paragraphs). Trueheart et al. also teach the ability of particular compounds to modulate a signal transduction activity of target receptor can be detected by a reporter gene (column 13, paragraphs 2-4; column 12, lines 44-54). Trueheart et al. further teach that the test compound can be a peptide, a small organic molecule (column 11, the 3rd paragraph), and can be derived from a peptide library or a non-peptide library (column 4, the 2nd paragraph).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Jubinsky et al. to functionally express

EPO-R and βc in a prokaryotic cell, such as a yeast cell, or a human cell to screen various compounds using a reporter gene taught by Trueheart et al. to identify a compound that modulates a tissue protective activity of the EPO-R/βc complex with a reasonable expectation of success. One would have been motivated to do so because the assay system provides a rapid, reliable and effective assay for screening and identifying effectors of a receptor protein or complex thereof as taught by Trueheart et al. (the 3rd paragraph of column 2; 2nd paragraph of column 13), Moreover, it would have also been obvious to one having ordinary skill in the art at the time the invention was made to screen a test compound, which is an antibody specific for a tissue protective cytokine receptor complex or a ligand thereof, or to screen a compound that binds the tissue protective cytokine receptor complex ligand because these compounds might act as a modulator of the a tissue protective activity of a tissue protective cytokine receptor complex. It is noted that the compound that modulates the activity of the EPO-R/βc complex screened by the method taught by the cited art would necessarily have the properties cited in claims 51-54.

(iv). Response to Applicants' argument

Beginning at page 8 of Applicants' response filed on 07/28/2008, Applicants cite case law and review the legal standard for obviousness, with which the examiner takes no issue.

At page 10 of Applicants' response, Applicants argue that Jubinsky et al. did not suggest that EpoR and βc form a receptor complex that mediated tissue protective activity and that Jubinsky et al. did not determine a necessary role for βcin the Epo-dependent survival.

Applicants' argument has been fully considered, but is not deemed to be persuasive because Jubinsky et al. teach that Epo-R physically associates (beginning at the bottom of right column of page 1869) with βc and form a receptor complex as shown in the coimmunoprecipitation experiment (Fig. 4). Even the title of the publication of Jubinsky et al. suggests that Epo-R and βc and form a receptor complex. The instant application also acknowledges that the Epo-R has been known to form a complex with βc (top of page 3). Moreover, Jubinsky et al. teach that both Ba/F3-Epo-R and at Ba/F3-EPO-R+βc required EPO for survival, and the Ba/F3-EpoR+βc had a greater proliferative response to Epo than Ba/F3-Epo-R (see, e.g., bottom of right column of page 1868; Fig. 1). Thus, Jubinsky et al. teach a tissue protective role for a functional complex comprising EPO receptor (EPO-R) and a common β chain (βc) in murine Ba/F3 cells (see specification at paragraphs [0006], [0091], [0037]).

At the 4th paragraph of page 10, Applicants argue that Jubinsky et al. fail to demonstrate any functional role for βc in the EpoR proliferative pathway in vivo. Applicants argue that Jubinsky et al. attempted to provide a possible explanation for why both Nishinakamura and Stanley saw no changes in responsiveness to EPO in animals that lack either βc or

βIL-3 receptor genes by raising the possibility that EPO interacts with non-disrupted β chain in these mice.

Applicants' argument has been fully considered, but is not deemed to be persuasive because Applicants' argument is irrelevant to the issue here. The instant claims are drawn to an *in vitro* screening method for a compound that modulates a tissue activity, whereas Jubinsky et al. teach a functional role of βc in the EPO-dependent proliferation of Ba/F3 cells that express EPO-R (see, e.g., bottom of right column of page 1868; Fig. 1).

At page 11, applicants argue that Scott et al. (Blood 96;1588-1590, 2000) suggests that the findings of Jubinsky et al. lack significance because they could not be supported, and in fact they were disproved, by primary cell data.

Applicants' argument has been fully considered, but is not deemed to be persuasive because multiple lines of evidence support the view that the βc chain functionally associates with the EPO-R and forms a EPO-R+βc complex (see, e.g., Hanazono et al., Biochem. Biophys. Res. Comm. 208:1060-1066, 1995; Jubinsky et al., Blood 90:1867-1873, 1997; D"Andrea et al., J. Clin. Invest. 102:1951-1960, 1998). In addition to the report of Jubinsky et al. that Epo-R physically associates with βc and form a receptor complex as shown in cultured Ba/F3 cells, D"Andrea et al. observed growth of CFU-E in the absence of Epo in spleen of transgenic animals where an activated form of the

human βc was expressed (Table IV). While Scott et al. report that there was no observed difference in responsiveness of $\beta c/\beta_{IL-3}$ null BM cells to EPO, the study of Scott et al. does not rule out a functional role of βc because it is well known that EPO binds to EPO receptor homodimers and promote cell proliferation, which may well explain the observed result of Scott et al.

Beginning at the bottom of page 11, Applicants argue that the finding that EPO interacted with βc to form a functional receptor complex that mediated tissue protective activity was entirely unexpected based on the teachings of Jubinsky and others at the time of the presently claimed invention. Applicants argue that it was not until the Applicants' discovery that the haematological activity of EPO could be separated from its tissue protective activity described in the instant application, that the claimed methods for identifying compounds that modulate tissue protective activity using tissue protective complex comprising an EPO receptor and a βc receptor were imaginable. Applicants argue that Applicants first found that a limited class of tissue protective cytokines modulate tissue protective activity through a receptor pathway that does not involve the classical EPO receptor dimmer. Applicants also argue that Applicants successfully extrapolated their findings to primary cell cultures, demonstrating that cardiomyocytes isolated from βc (-/-) knock out mice lack tissue protective activity in response to EPO. Applicants argue that one of ordinary skill in the art would not have been motivated to combine Jubinsky with either Trueheart or Mercury with any reasonable expectation of success of arriving at the invention as claimed in claims 13,1

4, 16-19, 20-212, and 43-50.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the instantly claimed invention is drawn to a cell-based in vitro screening method for identifying a compound that modulates a tissue activity using tissue protective complex comprising an EPO receptor and a βc receptor. The claims do not recite any particular signal transduction pathway, any particular tissue protective activity, or any feature that distinguishes the claimed subject matter from the teachings of the cited prior art. The claims do not limit the cells to cardiomyocytes isolated from βc (-/-) knock out mice.

Second, Jubinsky et al. teach that Ba/F3-EPO-R+βc required EPO for survival and (see, e.g., bottom of right column of page 1868; Fig. 1) and a functional role of βc in the EPO-dependent proliferation of Ba/F3 cells that express EPO-R. Jubinsky et al. teach a method for identifying the effect of antisense to βc, sense, and nonsense on EPO-dependent proliferation and β globin expression in Ba/F3 cells (page 1869; Fig. 2). Thus, Jubinsky et al. teach a cell system that can be used to identify a compound that modulates the proliferative activity of EPO-R/βc in BaF3 cells. The EPO-dependent proliferation would be considered to be a tissue protective activity in view of the disclosure of the instant specification (page 5, [0011])).

Moreover, Jubinsky et al. do not teach away from the claimed invention. Jubinsky et al.

interpret the results on mice performed by others, discuss the possibility that EPO interacts with the non-disrupt chain, and explain why both Nishinakamura and Stanley saw no change in the test animals' responsiveness to EPO despite the lack of either βc or βIL-3 receptor gene. Thus, in view of the teachings of the prior art, one of skilled in the art would have been motivated to combine Jubinsky with either Trueheart or Mercury with reasonable expectation of success of arriving at the invention as instantly claimed.

At the bottom of page 12, Applicants argue that newly added claims 51-54 are non-obvious over the prior art. Applicants argue that Nothing in Jubinsky, taken alone or combined with other cited art, suggest the limitations of the new claims. Applicants' argument has been fully considered, but is not deemed to be persuasive because since the cited prior art teach in combination the method of claims 13 and 21, the compound that modulates the activity of the EPO-R/βc complex screened by the method taught by the cited art would necessarily have the properties cited in claims 51-54.

Claim Objections—Minor Informalities

Claim 50 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 50 recites a limitation of "wherein the compound binds the tissue protective cytokine receptor complex ligand", which does not further claim 44. Appropriate correction is required.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646

Ruixiang Li, Ph.D.
August 16, 2008